Reducing mortality in individuals at high risk for advanced melanoma through education and screening

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Healthcare providers continue to underreport melanoma even though cancer reporting requirements mandate such reporting. Additionally, providers may be unaware of recent trends and descriptive epidemiology regarding melanoma which includes the fact that nonwhites have a higher mortality rate from melanoma than do whites.

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Incidence and mortality rates of melanoma throughout most of the developed world have increased in the past 25 years. We propose that reduction of deaths from melanoma can be best enhanced by strong collaborations between experts in dermatology, primary care, oncology, cancer education and health systems research, epidemiologists, and behavioral scientists, among others. Public and professional educational campaigns should be guided by an understanding of 3 underlying but overlapping roots: *epidemiology and preventable mortality* (an understanding of who is most likely to be given the diagnosis of thick or late-stage melanoma), *biology* (an investigation of tumor types that are relatively common but potentially most lethal), and *sociology* (an analysis of the changes needed in social structures to improve access to those most in need of early detection programs). We review these major concepts, concentrating on the key risk factors for advanced melanoma. (J Am Acad Dermatol 2011;65:S87.e1-9.)

Key words: early detection; education; melanoma; physician; screening; skin cancer.

Melanoma incidence and mortality rates throughout most of the developed world have increased sharply in the past 3 decades,[1-4] whereas education and screening continue to be underused.[5]

We highlight emerging incidence and mortality trends, provide data supportive of public health interventions to reduce melanoma mortality, and explore options for reducing mortality including screening trials and public and professional education to promote early detection of disease.

We propose that reducing melanoma mortality will best be accomplished through early identification, education, research, and advocacy. There also needs to be a focus on the emerging disproportionate burden of melanoma mortality and late-stage disease among white men ages 50 years and older and those persons of lower socioeconomic status (SES) and a practical understanding of physician practice patterns; multiple studies uniformly agree that physicians find thinner melanoma than the patient or their partners.[6] Such evidence points to the need for a strategy that improves the percentage of primary care physicians who are skilled and devote themselves to routine examination of the skin.

CAPSULE SUMMARY

- Middle-aged and older men and persons of low socioeconomic status have disproportionately high rates of advanced melanoma.
- Education and screening need to be focused and targeted to groups at most risk.
- Public health campaigns to reduce deaths from melanoma must be collaborative across multiple disciplines.

RISK FACTORS FOR ADVANCED MELANOMA

In contrast to other preventable cancers for which mortality has markedly decreased since 1975, melanoma mortality has only recently stabilized,[1,4] likely because fewer than a quarter of Americans report receipt of a skin examination.[5]

Middle-aged and older men, persons of lower SES, and individuals given the diagnosis of the nodular melanoma (NM) subtype are at greatest risk of advanced disease.

Middle-aged and older men

As described by Jemal et al[4] and Watson et al[7] in this supplement, disproportionate mortality is driven by unabated increases in the incidence rate for middle-aged and older men. For example, since 1975, incidence rates have more than doubled for men ages 50 to 59 years, quadrupled for men ages 60 to 69 years, and multiplied 7-fold for the oldest men, ages 80 years and older.[4]

Hispanics

Although melanoma diagnoses are rare in persons of color,[8,9] reports presented in this supplement find

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Abbreviations used:

AAD: American Academy of Dermatology
CI: confidence interval
NM: nodular melanoma
OR: odds ratio
QALY: quality-adjusted life year
SES: socioeconomic status
SSE: skin self-examination
SSM: superficial spreading melanoma

increasing incidence rates and a greater proportion of thick lesions among Hispanics.[10] Furthermore, a recent analysis of melanoma incidence among those who self-identified as Hispanic and non-Hispanic white patients in California has demonstrated that lower SES is more strongly associated with thicker tumors (>2 mm) in Hispanics compared with whites (relative risk 2.18, 95% confidence interval [CI] 1.73-2.74 vs 1.48, 95% CI 1.37-1.61, respectively).[11] Compared with higher SES patients, lower SES male Hispanic patients had fewer superficial spreading melanomas (SSM), more nodular and acral lentiginous melanomas, and more frequent leg and hip melanomas.[11]

Social class and melanoma

The data presented by Singh et al[12] in this supplement describe the association between the SES of a given area and melanoma incidence. Earlier, Reyes-Ortiz et al[13] summarized the studies related to the effect of SES on melanoma stage at diagnosis rather than incidence alone. Of the 12 studies analyzed (8 population-based), all found increased rates of advanced-stage melanoma or decreased survival in lower SES individuals. Various indices of social class were used including occupation, education, physician supply, and poverty rates.[13] Using Surveillance, Epidemiology, and End Results and California Cancer Registry data (1988-2004), Linos et al[14] found an increasingly higher rate of thicker, poor-prognosis melanomas for persons of lower SES. Pollitt et al[15] linked California Cancer Registry records with Medicaid enrollment status and found that late-stage disease was diagnosed in 27% of Medicaid enrollees compared with only 9% of non-Medicaid enrollees statewide.[15]

Individuals given the diagnosis of NM

Worldwide, the NM subtype accounts for a disproportionate number of newly diagnosed thick melanoma ($\geq$2 mm). In an analysis of more than 35,000 invasive melanomas from the National Cancer Institute Surveillance, Epidemiology, and End Results data (1988-1999), NM comprised only 9% of all lesions but accounted for nearly 50% of melanomas 2 mm or deeper when melanomas not otherwise specified were excluded. Median thickness of NM changed little from 1988 to 1991 (2.14 mm) through 1995 to 1999 (2.16 mm) and NM were nearly 4-fold thicker than SSM (0.54 mm, median thickness).[16]

To assess differences between Queensland, Australia patients with thin ($\leq$2.00 mm) and thick ($\geq$2.01 mm) NM, Geller et al[17] evaluated factors such as demographics, melanoma detection patterns, tumor visibility, and physician screening for NM alone and compared clinical presentation and anatomic location of NM with SSM. During this 4-year period, 369 patients with NM were interviewed, of whom 57% were given a diagnosis of melanoma less than or equal to 2.00 mm. Men, older individuals, and those who had not been screened by a physician in the past 3 years were more likely to have nodular tumors of greater thickness. The thickest NMs ($\geq$4 mm) were also most common in individuals who had not been screened by a physician within the past 3 years (odds ratio [OR] 3.75; 95% CI 1.47-9.59). Of patients, 46% with thin NM ($\leq$2.00 mm) reported a change in color, midway between patients with thin SSM (64%) and patients with thick NM (>2.00 mm) (26%).[17] Most recent dermatoscopic analyses of thin NM found them to have characteristics such as a blue-white veil, structureless areas, and atypical vascular structures.[18]

REDUCING MORTALITY VIA EARLY IDENTIFICATION AND EDUCATION

Four complementary strategies for the reduction of melanoma deaths are reviewed: (1) conduct of early detection trials, (2) clinician education, (3) NM research, and (4) targeted education for reaching population subgroups at greatest risk of advanced-stage disease.

Conduct of early detection trials

Organized efforts to detect melanoma early are ongoing and can be enhanced in multiple venues, such as community-wide screenings, dermatology-led mass screenings, nondermatologist physician or health care professional surveillance, skin self-examination (SSE), specialized pigmented lesion clinics, and via public education targeted to individuals at greatest risk for this disease.

Most recently, the US Preventive Services Task Force concluded that evidence is lacking that routine skin examination of the adult general population by primary care clinicians is effective in reducing mortality or morbidity from skin cancer in the general population.[19] English-language studies were selected by the Task Force to answer the following key question: Does screening in asymptomatic persons with whole-body examination by a primary care clinician or by

self-examination reduce morbidity and mortality from skin cancer?[19]

In consideration of a randomized trial in the United States, estimated costs and numbers needed to screen were recently projected.[20] Based on current melanoma incidence and mortality, a randomized trial of melanoma screening with a 20% impact on mortality would require a screened study population of 350,000 Americans (and 700,000 control subjects) ages 45 years and older with a 4-year intervention period and 8 years passive follow-up at an estimated cost of $30 million to $40 million. Large-scale trials have used mortality as proper end points. However, with compelling data confirming the usefulness of tumor thickness and stage of disease as a proxy for mortality, melanoma severity (with tumor thickness and/or sentinel lymph node positivity as key components) should be addressed as part of any cost projections.[20]

Numerous attempts have been made to collect evidence demonstrating the effectiveness of melanoma screening. These include in chronologic order: screening of self-selected individuals in the American Academy of Dermatology (AAD) programs in the United States,[21,22] the Lawrence Livermore National Laboratory Study,[23] a community randomized trial in Australia,[24-26] and national screening in Germany.[27] Major studies have also included a recent case-control study in Australia and cost-effectiveness modeling.[28,29] These are briefly reviewed.

The AAD free skin cancer screening programs have reached more than 1.5 million Americans. Of screenees, 65% had at least one risk factor for melanoma and 33% reported a changing mole. Among all screenees, nearly 80% did not have a regular dermatologist, 78% reported no prior AAD skin cancer screening, 60% had never had their skin checked by any doctor, and 51% reported that they would not have seen a doctor for skin cancer without the free screening. Among nearly 250,000 screenees, 363 melanomas were diagnosed—98% of which were stage I melanomas.[21,22] In other settings, workplace screening at the Lawrence Livermore National Laboratory yielded a progressive decreasing incidence of thicker melanoma and subsequently no melanoma deaths during the intensive screening program.[23]

The higher rates of melanoma in Australia allowed researchers to plan and implement a randomized trial of population screening.[24-26] Although the plan called for randomizing a total of 44 Queensland, Australia, communities, only 18 were initially randomized to intervention (n = 9) and control (n = 9) towns before the study funding was withdrawn. The trial's 3 components included: (1) a community education component, which aimed to provide accurate information about melanoma and screening to residents; (2) an education and support component for medical practitioners, which aimed to increase awareness of the program and to improve doctors' skills in screening for and diagnosing melanoma; and (3) the provision of free skin screening services.[24-26] Uptake of the whole-body skin cancer examination was measured by surveys of residents in intervention and control towns. Baseline rates were similar in intervention and control towns (11.2% and 11.3%); however, rates jumped 2 years later to 34.8% in intervention towns while remaining constant (13.9%) in control communities.[26] In general, screenings were performed by general practitioners. Tumor thickness is unknown. Community-based or clinic-based randomized studies with tumor thickness or mortality end points are needed.

In Germany, a major skin cancer screening program is underway. The goal is to screen every citizen ages 35 years and older (45 million individuals) and to date, more than 10 million examinations have taken place; the major outcome will be reduction in mortality in the period before and upon completion of the screening program. The goal of training the nation's 45,000 physicians with an 8-hour training program has been nearly reached.[27]

Aitken et al[28] reported results from a population-based case-control, telephone-based study of all Queensland, Australia, residents aged 20 to 75 years with a histologically confirmed first primary invasive cutaneous melanoma diagnosed between January 2000 and December 2003. Whole-body clinical skin examination in the 3 years before diagnosis was associated with a 14% lower risk of being given a diagnosis of a thick melanoma (>0.75 mm) (OR 0.86; 95% CI 0.75-0.98). Screening was associated with a 38% higher risk of being given a diagnosis of a thin invasive melanoma ($\leq$0.75 mm) (OR 1.38; 95% CI 1.22-1.56). This is the strongest evidence to date that whole-body clinical skin examination reduces the incidence of thick melanoma and these results suggest that screening would reduce melanoma mortality.[28]

In a cost-effectiveness model, Losina et al[29] found that one-time melanoma screening of the general population was cost-effective compared with other cancer screening programs in the United States. In the general population, one-time, every 2-year, and annual screening saved 2.5, 8.8, and 10.2 quality-adjusted life years (QALY) per 1000 people screened, with incremental cost-effectiveness ratios of $7300/QALY, $58,000/QALY, and $450,500/QALY for one-time, every 2-year, and annual screening, respectively.[29]

Table I. Professional education: Rationale for primary care provider's role in early detection

- Most Americans do not have a dermatologist
- Only 25% of white Americans have been screened
- Middle-aged and older men make at least 3-4 visits per year to a physician or medical care facility
- Nearly 2/3 of cases report seeing physician in year before diagnosis
- Many lesions are not easily visible to patient

Only one study has tested mortality reduction associated with SSE. Berwick et al[30] conducted a case-control study and found that SSE could potentially reduce mortality as a result of melanoma by 63%. Two other observational studies have been conducted. More recently, SSE was found to be a key predictor for melanoma less than 1 mm in thickness.[31] In a study of 321 dermatology clinic patients, Pollitt et al[32] found that using a melanoma picture as a SSE aid was strongly associated with reduced tumor thickness (adjusted ratio 0.75; 95% CI 0.66-0.85). Whether patients can consistently find early melanoma, particularly on hard-to-see sites, is questionable and deserves further scrutiny.

Janda et al[33] recently reported on the successful recruitment of men aged 50 years or older to a randomized trial using a 12-minute intervention video toward men 50 years or older. Of more than 900 men recruited for the study, 13% reported conducting a whole-body SSE and 39% reported receiving a full-body clinical skin examination by a doctor within the past 12 months, with confidence in finding time for SSE and receiving physician instruction for SSE related to thorough SSE at baseline.

Clinician education

Full-body examinations by either dermatologists or nondermatologist physicians have both shown the potential to save lives otherwise lost to melanoma. Of the 5 major early detectable cancers (melanoma, breast, colorectal, prostate, and cervical cancer), only skin cancer requires an initial visual, noninvasive examination.

The rationale is strong for an educational outreach campaign to primary care providers (Table I). Most Americans do not have a dermatologist and only 25% of Americans report ever being screened for melanoma.[6] Middle-aged and older men make at least 3 to 4 visits to a physician annually and nearly two thirds of cases report seeing a physician in the year before diagnosis.[34,35] Moreover, many lesions are on hard-to-see sites and this finding provides some insight into why melanoma is discovered earlier by physicians compared with the patient or their partner.

Many recent studies have analyzed tumor thickness by melanoma detector, such as the patient, their partner, or the physician (dermatologist or nondermatologist physician). Nearly all of the studies have found a favorable tumor thickness for melanoma diagnosed by primary care providers at least 0.5 to 1.00 mm thinner.[36,37] In a study of cases diagnosed in Michigan and California, 69% of physician-diagnosed melanomas were less than 1 mm compared with 33% of self-detected melanomas.[36] However, less than half of US physicians routinely examine the skin for cancer, and neither medical students nor primary care residents are adequately trained in skin cancer examination.[38-41]

Much remains unknown about melanoma discovery patterns and differences between dermatologist and primary care provider biopsy and referral practices. Chen et al[42] performed a systematic review of 32 studies of melanoma discovery patterns conducted before 2001 and found numerous information gaps, including lack of consistent sensitivity and specificity data, inadequate sample sizes, and data derived primarily from residents rather than attending physicians.

Although there are a number of factors promoting physician-led screening, many barriers persist. In a regression analysis of factors influencing physician examination of patients at high risk, lack of time was the strongest barrier (OR 0.3; 95% CI 0.2-0.6). Physicians using the most information sources, such as brochures (OR 2.5; 95% CI 1.3-4.8) were the most inclined to examine their patients at high risk (risk factors included: fair skin, many moles, a few atypical moles, family and/or personal history of skin cancer, and excessive sun exposure). Physicians whose patients requested a skin examination were more likely to examine their patients compared with physicians whose patients did not request such an examination ($P < .01$).[39] Therefore, an educational campaign that encourages Americans at high risk to request a thorough screen by their primary care provider during the routine medical examination may be warranted.

A number of new World Wide Web sites are dedicated toward improving the recognition and triaging of skin lesions by primary care physicians.[43,44] Curricula innovators are trying to establish educational programs tailored to physicians to encourage them to integrate a thorough examination as part of the routine medical visit. For example, at least 30% of all lesions in men are on the back and an estimated 20% of all melanomas in women are on the back of the legs.[45] Examining lesions on the back

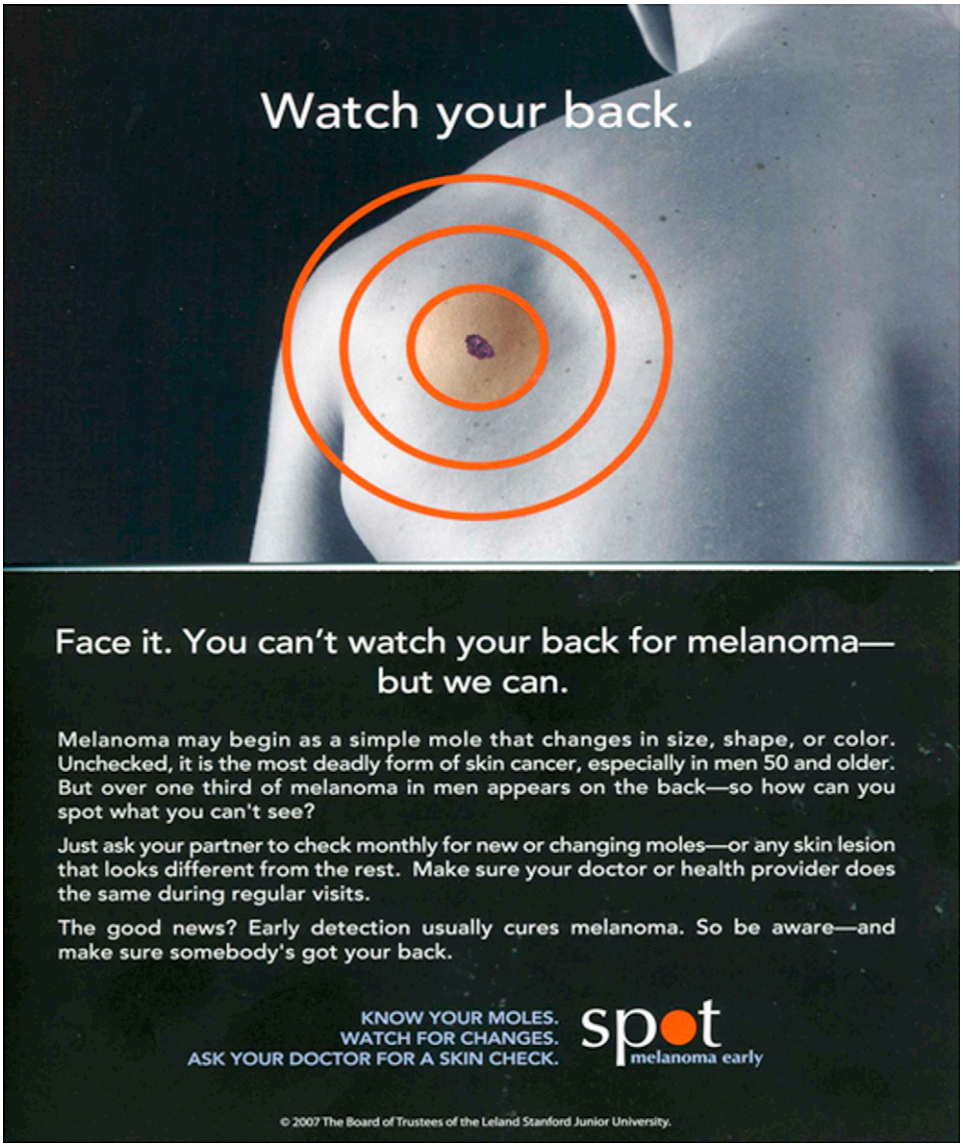

Fig 1. Campaign to improve recognition of back melanoma. Printed with permission.

(Fig 1) while listening to the lungs or performing a cardiac examination should be mainstays of a new educational curriculum. Ancillary personnel such as hairdressers and masseuses can be trained to survey the scalp and back for suspicious lesions.

Nodular melanoma

With the NM subtype comprising a disproportionate share of thick melanoma histology, more research is needed to distinguish tumor and other factors related to thin versus thick NM at presentation. The fact that nearly 50% of all NM are diagnosed at less than 2 mm and that they possess clinical signs akin to SSM provides reason to believe that there is a detectable preclinical phase for earlier detection.[16] Multifactorial studies should examine differences at the molecular, epidemiologic, and behavioral levels for this rapidly growing subtype.

Focused advocacy

Understanding the role that gender and social class play in melanoma knowledge, attitudes, access to an initial screening examination, discovery, and diagnosis is central to narrowing the striking economic and gender divide. Middle-aged and older men, persons of lower SES, and individuals with lack of access to skilled personalized care are all at greater risk of advanced-stage disease. Although there are more than 50 melanoma foundations in the United States, few focus exclusively on early detection. With recent analyses finding increasing rates of melanoma among young women,[46] they too should be

Table II. Proportion of melanoma classified by tumor thickness—United States 1988 to 2006[56]

Tumor thickness, mm	No. of cases	No. of deaths	Cases/ death	Percent of deaths
<1	91,174	2472	37	27
1.01-2	20,424	2142	9.5	23
2.01-4	11,702	2474	4.7	27
>4	6894	2041	3.7	22

considered at high risk in need of education regarding the dangers of tanning.

For the high-risk demographic of older men, the 2000 Institute of Medicine report noted that evidence does support the benefits of early melanoma detection and treatment as part of usual medical care but noted that "clinicians and patients should continue to be alert to the common signs of skin cancer."[47] Special efforts to reach men ages 50 years or older led to increased screening as part of the Queensland, Australia, community-based trial. Men ages 50 years or older comprised 21% of all participants but accounted for 49% of all melanoma diagnoses.[48] A famous Australian cricket player's letter as part of an overall promotion packet was instrumental in boosting screening rates.

Multiple factors are key to achieving access to high-quality examinations for at-risk patients. Access to a consistent primary care practice is essential for the detection of early melanoma. Researchers in Nova Scotia used a billing system to examine access and continuity with family practitioners and its association with melanoma thickness. Patients with multiple visits to the same physician (rather than to many different providers) had a lower risk for having a thicker than 0.75 mm melanoma at time of diagnosis.[49] Access to care is also illustrated by recent studies using Medicare data showing that diagnosis by a dermatologist (as opposed to nondermatologist physicians) more favorably correlates with melanoma survival at 2 years.[50] In a study of 42 counties in North Carolina, which included many rural counties, Stitzenberg et al[51] found that greater distance from an individual's home to a dermatologist was associated with advanced tumor thickness. They speculated that proximity to dermatologic care was an indicator of local health resources and noted that patients who lived in counties with at least one dermatologist traveled less for care than did patients in communities with fewer dermatologists. In the United States, mortality of melanoma appears to be higher in states with fewer dermatologists and in more rural areas.[52]

Combining Florida state tumor registry data with state physician data found that each additional dermatologist per 10,000 residents was associated with a 39% increased likelihood of earlier diagnosis. Roetzheim et al[53] suggested that AAD screenings branch out to areas with the shortest supply of dermatologists. In a study using US National Health Interview Survey data, having health insurance and a usual source of health care were important predictors for skin cancer screening with few differences between men and women.[54] A United Kingdom study found reluctance to seek advice for a suspect lesion was most pronounced among persons from socially deprived districts, suggesting that there could be significant attitudinal barriers to screening among certain groups.[55]

CONCLUSIONS

Lessening the burden of melanoma mortality requires a better understanding of the factors that lead to potentially avoidable mortality as a result of melanoma. Using a match between tumor thickness (the most well-established prognostic measure for melanoma mortality) and fatal melanomas, Criscione and Weinstock[56] examined the proportion of US melanoma deaths classified by tumor thickness and found that 50% of all melanoma deaths occur in persons with melanoma diagnosed at 2 mm or less. The case fatality rate changes markedly for melanomas diagnosed at less than 1 mm (1 death/37 cases) compared with 1 death per 10 cases for melanomas diagnosed between 1.01 and 2.00 mm. The extent to which modifiable and behavioral factors play a role in delayed diagnosis, late treatment, or late discovery of lesions merits further study and holds an important key to reducing unnecessary deaths from melanoma (Table II).[55] Most importantly, strong differences in case fatality between lesions less than 1 mm versus those between 1 and 2 mm requires a full-scale campaign (using tools such as dermatoscopy) to detect most curable melanomas. Currently, tumor thickness is collected in some but not all cancer registries, and data are not reported nationally. Comprehensive collection and reporting of this variable would enable improved surveillance of melanoma detection, especially in states with few dermatologists and in more rural areas.

Low screening rates in the presence of persistently increasing but avoidable mortality prompt a call for broad-scale and innovative approaches, including ways to make screening more available to underserved individuals, targeted education to the high-risk public, and early professional education to health professional students in all disciplines.

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